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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/747,686	12/30/2003	Mitchell S. Steiner	P-2769-US9	2903

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EXAMINER

FUBARA, BLESSING M

ART UNIT	PAPER NUMBER
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1618

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/12/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary

Application No.

10/747,686

Applicant(s)

STEINER ET AL.

Examiner

Blessing M. Fubara

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 30 December 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-32 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-32 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date <u>7/31/06</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Examiner acknowledges change of address filed 6/2/06 and IDS filed 7/31/06. Claims 1-32 are pending.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1-32 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is scope of enablement/written description.

Scope of enablement is considered in view of the Wands factors (MPEP 2164.01(a)).

The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.'" (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: 1) Nature of

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invention, 2) State of prior art, 3) The predictability or lack thereof in the art, 4) Amount of direction and guidance present, 5) The presence or absence of working Examples, 6) Breadth of the claims, and 7) Quantity of experimentation needed. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

Inhibiting pre-malignant lesions of prostate cancer in a human as it applies to prevention is addressed below.

1) Nature of the invention.

The nature of the invention is directed to methods of inhibiting the incidence of pre-malignant lesions of prostate cancer (intraepithelial neoplasia (PIN) and high grade prostate intraepithelial neoplasia (HGPIN) by administering a known drug to a human subject.

There is no one treatment, or combination of treatments, which provides inhibition (not occurring even the first time) of PIN/HGPIN. The best prevention, however, is a life-long commitment to physical activity, good nutrition, and normal prostate wellbeing. (See <http://www.prostate-disorders.com/html/pin.php3>), however, this is not prevention, as described in the article.

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. Further, their mode of action is often unknown or very unpredictable and administration of the drugs can be accompanied by undesirable side effects.

2) State of the prior art and the predictability or lack thereof in the art.

The state of the prior art is that it involves a myriad tests to determine the presence of PIN and to determine the stage of the PIN so that inhibiting or treating will include screening *in vitro* and *in vivo* to determine the effect of the compound on the specific disease state. There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face. The instant claimed invention is highly unpredictable as discussed below:

Thus, in the absence of a showing of correlation between all the conditions associated with PIN claimed as capable of being treated/prevented/suppress by the compounds of the instant claims, one of ordinary skill in the art is unable to fully predict possible results from the administration of the compounds due to the unpredictability of the role of predisposition and other latent factors and causes, for example.

3) Quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The quantity of experimentation needed is undue experimentation. One of ordinary skill in the art would first need to determine the type of conditions associated with PIN, **predisposition and other factors** and then determine when to administer the composition comprising the drug and also to the level needed to effectively prevent/suppress/treat the recurrence of PIN.

4) Level of predictability in the art.

The art pertaining to the treatment of all PIN/HGPIN remain highly unpredictable. As disclosed above, there is no absolute predictability even in view of the seemingly high level of

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skill in the art. Treatments for conditions associated PIN are normally tailored to the particular type of mediator present, patient and patient compliance. There is no, and there can be no “magic bullet” against all conditions associated with PIN/HGPIN and other related conditions.

Therefore, the specification fails to provide sufficient support of the broad use of the compositions of the claims for inhibition of any PIN/HGPIN at any stage and in all cases necessitating one of ordinary skill in the art to perform an exhaustive search to determine what stage of the diseases can be treated/suppressed/prevented the instant claimed composition in order to practice the claimed invention.

In view of the lack of guidance, working examples, breadth of the claims, the level of skill in the art and state of the art at the time of the claimed invention was made, it would have required undue experimentation to make and/or use the invention as claimed.

It is noted that the specification must teach those of skill in the art how to make and how to use the invention as broadly claimed. In re Goodman, 29 USPQ2d at 2013 (Fed. Cir. 1994), citing In re Vaeck, 20 USPQ2d at 1445 (Fed. Cir. 1991).

The courts have stated that reasonable correlation must exist between scope of exclusive right to patent application and scope of enablement set forth in patent application. 27 USPQ2d 1662 *Ex parte Maizel*.

Scope of Enablement is considered in view of the Wands factors (MPEP 2164.01 (a)). In view of the quantity of experimentation necessary to determine the parameters listed above, the lack of direction or guidance provided by the specification, the absence of working examples for the demonstration or correlation to the scope of the claimed invention.

A lack of adequate written description issue arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from

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the disclosed process. See, e.g., *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1571, 39 USPQ2d 1895, 1905 (Fed. Cir. 1996)

An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

A "representative number of species" means that the species, which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. The disclosure of only one species encompassed within a genus adequately describes a claim directed to that genus only if the disclosure "indicates that the patentee has invented species sufficient to constitute the gen[us]."

In the present case, applicant claims metabolites/analogues of the triphenylethylene antiestrogenic compound depicted as formula (I) in claims 10 and 11. However, the

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specification merely mentions metabolites of the triphenylethylene antiestrogenic compound depicted as formula (I) without naming any of the metabolites. Secondly, the claims direct the use of the metabolites in formulation/dosage form for administration to a person for the claimed method. However, it is known that all metabolites are not all active, and metabolites can also be unstable. For example, DeGregorio in US 5,605,700 lists the following as metabolites of toremifene, one of the compounds that satisfies the generic compound of formula (I): **N-demethyltoremifene (4-chloro-1,2-diphenyl-[4-[2-(N-methylamino)ethoxy]-phenyl]-1-butene) or 4-hydroxytoremifene (4-chloro-1-(4-hydroxyphenyl)-2-phenyl-1-[4-[2-(N,N-dimethylamino)ethoxy]phenyl]-1-butene)**. The specification does not say, ---metabolites of compound of formula (I) are In addition, there is no exemplification or description of dosage forms comprising/containing any metabolite of the compound of formula (I). It will thus require the artisan to carry out undue experimentation to determine those metabolites known or future identified metabolites to practice the full scope of the claimed invention. Furthermore, the listing in paragraph 67 of the published application that analogs and/or metabolites are 4-chloro-1,2-diphenyl-1-[4-[2-- (N-methylamino)ethoxy]phenyl]-1-butene; 4-chloro-1,2-diphenyl-1-[4-[2-(N,N -diethylamino)ethoxy]phenyl]-1-butene; 4-chloro-1,2-diphenyl-1-[4(aminoethoxy)]-1-butene; 4-chloro-1-(4-hydroxyphenyl)-1-[4-[2-(N,N-dimethylamino)ethoxy]phenyl]-2-phenyl-1-butene; 4-chloro-1-(4-hydroxyphenyl)-1-[4-[2-(N-me- thylamino)ethoxy]phenyl]-2-phenyl-1-butene; and 4-chloro-1,2-bis(4-hydroxy- phenyl)-1-[4-[2-(N,N-dimethylamino)ethoxy]phenyl]-1-butene is an invitation to experiment with these compounds since there is no clear description of what is an analog and what is a metabolite. Further, it is stated in paragraph 67 that the above listed compounds are derived upon administration of

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toremifene. Thus by the above listing, and applicant's admission that the analog/metabolite is not limited to the listed 5 compounds, it would require undue experimentation to practice the full scope of the claimed invention.

Therefore as discussed above, applicant has not provided a description of the structure of a representative number of compounds nor a description of the chemical and/or physical characteristics of a representative number of compounds nor a description of how to obtain a dosage form or compositions containing the representative number of specific compounds that are metabolites of the compound of formula (I) that would be administered to practice the claimed method. In other words, the Applicant has not described with sufficient clarity **metabolites of the compound of formula (I) suppressing or inhibiting the incidence of premalignant lesions of prostate cancer.**

The specification does not also provide distinction between analogs and metabolites.

The above rejection may be overcome by claiming the metabolites or analogs that are disclosed and described in the specification that is applicable in the claimed method. Further, toremifene is one of the compounds that have the generic formula (I).

What are the analog and the metabolites of the other compounds that have the general formula (I)?

Does the invention claims 10 and 11 use analogs or metabolites of the compound of formula (I)?

Claim 12 recites those same compounds listed in paragraph and identifies them as the compound while claims 10 and 11 specifically require the use of analogs and metabolites of the compound of the formula (I).

Double Patenting

3. Claims 1-32 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3, 7, 45 and 54-67 of copending Application No. 10/611,056. Although the conflicting claims are not identical, they are not patentably distinct from each other because the same compositions are employed in the examined claims and the copending claims to suppress/inhibit/reduce the incidence of premalignant lesions or PIN/HGPIN.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

4. Claims 10-32 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-22 of copending Application No. 10/747,685. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claimed inventions are the same except that the examined application has analog in claims 10 and 11 and claims 1 and 2 of the co-pending application does not recite analog. However, later dependent claims 3-5 of the co-pending application 10/747,685 recite analog. The claims are not identical, but are inherently the same.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicant is reminded that there are several applications and issued patents that are subject to non-statutory obviousness double patenting rejections. It is therefore suggested to

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applicant to file all applicable terminal disclaimers or amend the claims to obviate any statutory double patenting in order to expedite prosecution and to avoid prosecutions in the applications rendered final in view of lack of appropriate actions from applicant.

No claim is allowed.

Other matters:

It appears that claim 13 intended to say "any of claims 10 and 11" and if this is the intended directive of the claim, ---and 11--- is missing from the claim. The same true for claims 14, 15.

5. The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Blessing M. Fubara whose telephone number is (571) 272-0594. The examiner can normally be reached on 7 a.m. to 5:30 p.m. (Monday to Thursday).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Hartley can be reached on (571) 272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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